REMARKS

Claims 1-14 are pending in this application. Claims 1 and 2 are currently amended in this Response.

Summary of Amendments to the Claims and Specification

The specification is amended to clarify the pH range with regard to the presently disclosed composition and method. No new matter is introduced in the specification because the added paragraph merely recites disclosure in another patent U.S. Pat. No. 5,514,200 (See Col. 4, lines 13-40 of U.S. Patent No. 5,514,200), which has been incorporated by reference into the present patent (See Col. 2, lines 20-30 of U.S. 5,997,910).

I. Claim Rejection under 35 U.S.C. § 112

Claims 4 and 10 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner maintains that claim 4 fails to further limit claims 1 and 3, while claim 10 fails to further limit claims 1 and 9. Applicant respectfully disagrees.

Claim 4 recites the concentration range of the first salt and second salt, and therefore does further limit the scope of claim 3. Similarly, claim 10 recites the concentration range of the first salt and second salt recited in claim 9, and therefore does further limit the scope of claim 9. Withdrawal of the rejections is requested.

II. Claim Rejection under 35 U.S.C. § 102(b)

Claims 1 and 2 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 4,350,770 issued to Spraker (hereinafter "Spraker"). Applicant respectfully disagrees because not all claim limitations of claims 1 and 2 are taught by Spraker.

Claim 1 of the instant application recites that the first and second salts are <u>each</u> present in solution from about 0.25% to about 5% vol./vol. By contrast, the salts

taught in Spraker, namely, KH_2PO_3 and K_2HPO_4, are present at 3 g/l and 9 g/l, respectively. The Examiner has not carried the initial burden to establish that the concentration range of the two salts in Spraker falls within the recited range of about 0.25% to about 5% vol./vol.

The density of KH_2PO_4 is 2.338 g/ml, and the density of K_3PO_4 is 2.564 g/ml. *See* page B-120, Handbook of Chemistry and Physics, 67th ed. (CRC Press, 1986-1987). If we assume that the density of KH_2PO_3 and K_2HPO_4 is 2.564 g/ml, the volume of KH_2PO_3 in Spraker is about 3/2.564 = 1.17 ml per liter, which translates to about 0.117% vol. vol. The volume of K_2HPO_4 is about 9/2.564 = 3.51 ml per liter, which translates to about 0.351% vol. vol.

On the other hand, if we assume that the density of KH_2PO_3 and K_2HPO_4 is 2.338 g/ml, the volume of KH_2PO_3 in Spraker is about 3/2.338 = 1.28 ml per liter, which translates to about 0.128% vol./vol. The volume of K_2HPO_4 is about 9/2.338 = 3.84 ml per liter, which translates to about 0.384% vol./vol.

Note that the concentrations of the <u>phosphonate</u> salt in Spraker are at a range of about 0.117% to 0.128% vol. /vol., which is significantly lower than the phosphonate concentration recited in Claim 1, namely, about 0.25% to about 5% vol. /vol. Although the phosphate concentration in Spraker may fall within the recited range of 0.25% to about 5% vol. /vol., because Claim 1 requires that <u>each</u> said first and second salts need to be present in solution from about 0.25% to about 5% vol./vol., Spraker does not teach or suggest this claim limitation.

Claim 2, as amended, recite that the pH of the solution is from 5-7, which is not disclosed in Spraker. Indeed, the solution of Spraker is a basic salt solution. See lines 60-61, Col. 10 of Spraker. Thus, because Spraker does not disclose all claim limitations of Claims 1 and 2, it does not anticipate Claims 1 and 2. Withdrawal of the 102(b) rejections are respectfully requested.

III. Rejections of Claims 1, 2, 6 and 12 under 35 U.S.C. § 103(a)

Claims 1, 2, 6 and 12 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Fenn et al '84 and Dolan et al. '88, with evidence exemplified by Barlet-5070083. Applicant respectfully disagrees because substantial difference exist

between the cited references and the instant invention and these differences are not obvious to one of ordinary skills in the art at the time of the present invention.

The rejections fail to take into consideration the failure among the research community to account for the effects of phosphate and phosphite salts in inhibiting fungal infection in plants. Dolan and Fenn produced contradictory data with respect to the influence by phosphate on the fungicidal effects of phosphorous acid and at most demonstrate that the relationship between phosphate and phosphite concentrations and their effects on infection inhibition may be very complex. Another reference of record, Griffith, which is not cited by the Examiner in the instant Office Action attempts to explain why Fenn and Dolan contradict one another. J. M. Griffith, M.D. Coffey, and B.R. Grant 1993, "Phosphonate inhibition as a function of phosphate concentration in isolates of *Phytophthora palmivora*," J. OF GENERAL MICROBIOL., 139: 2109-2116. After comparing the sensitivity of different fungi to phosphonate at different concentration of phosphate, Griffith suggests that relatively high concentrations of phosphate diminish the antifungal effects of phosphonate. Thus, at the time of the present invention, the use of relatively high concentrations of phosphate and phosphonate such as those claimed in the instant claims as a fungicidal or growth-stimulating agent was a surprising discovery by Applicant.

The Examiner has acknowledged that the compositions disclosed in either Fenn or Dolan are much more dilute than the compositions of the present application. The Examiner cited Figures 1 and 5 of Fenn and Figures 1-3 of Dolan and reasoned that because the dose/response curves in Fenn and Dolan showed enhanced efficacy, one of ordinary skills would be motivated to increase the concentration of PO_3 or PO_4 in the composition. However, none of the dose/response curves in Figures 1 and 5 of Fenn and Figures 1-3 of Dolan show a combined first salt of PO_3 and second salt of PO_4 as instantly claimed. Even if one would be motivated to extrapolate from the curves of Figures 1 and 5 of Fenn and Figures 1-3 of Dolan, one would only arrive at a composition with a higher concentration of PO_3, but not the claimed composition with much higher concentrations of both PO_3 and PO_4.

Although Dolan and Fenn did study the effect of phosphate on the inhibition of infection by phosphorous acid, the two papers produced contradictory results with

respect to the influence by phosphate on the fungicidal effects of phosphorous acid. For instance, Table 4 of Fenn (below) shows that increasing the phosphate concentration in the presence of phosphonic acid reduced the percent of inhibition. This was true of all seven genera of fungus as well as *Phytophthora cinnamomi*, where even the addition of 100X more phosphate diminished the reported inhibition from 100% to 90%. Thus, Fenn actually teaches away from the present invention which teaches a much higher concentration of both PO_3 and PO_4 in the same composition.

TABLE 4. Percentage growth inhibition of various fungi on Ribeiro's synthetic agar medium (RMSM) containing 0.84 mM H_3PO_3 (69 $\mu g/ml$) at three phosphate concentrations

Fungus	Percentage inhibition of radial growth[a] at KH_2PO_4 concentrations (mM) of: 0.084	0.84	8.4
Phytophthora cinnamomi (Pc356)	100 a	93 a	90 a
Pythium aphanidermatum	53 b	56 b	31 b
Rhizopus stolonifer	52 b	30 c	0 c
Fusarium oxysporum f. sp. *apii*	42 b	5 d	1 c
Verticillium dahliae	49 b	0 d	1 c
Schizophyllum commune	38 b	0 e	2 c
Rhizoctonia solani	3 c	0 e	0 c

[a]Percentage based on colony growth on identical medium without H_3PO_3. Values are means of four or five replications. At a particular KH_2PO_4 concentration, values with the same letter are not significantly different according to Duncan's multiple range test ($P = 0.05$).

Dolan presents data using similar concentrations where tomato seedlings were inoculated with *Phytophthora palmivora* to assess the effects of increasing phosphate content upon fungal infection rate. The relevant results are shown in Dolan's Table 4 below:

TABLE 4. Effect of 1 or 10 mM potassium phosphate levels on the percent inhibition of infection of tomato seedlings treated with phosphorous acid (H_3PO_3) or fosetyl-Na and inoculated with either the parental isolate of *Phytophthora palmivora* (PO376) or a mutant strain (L3) exhibiting high resistance to H_3PO_3

Treatment (PO_3 meq/L)[z]	Phosphate level (mM)	Percent inhibition of infection[y]			
		PO376		L3	
		H_3PO_3	Fosetyl-Na	H_3PO_3	Fosetyl-Na
0.85	0	57 d	6 g	17 f	0 c
2.43		100 a	36 e	59 c	0 c
6.10		100 a	100 a	71 b	2 c
0.85	1	72 c	19 f	39 e	3 c
2.43		100 a	42 d	48 d	4 c
6.10		100 a	99 a	73 b	3 c
0.85	10	87 b	69 c	45 de	39 b
2.43		100 a	91 b	75 b	45 a
6.10		100 a	100 a	82 a	45 a

[y] Bare-rooted seedlings were placed in solutions of H_3PO_3 and of fosetyl-Na with 0, 1, or 10 mM potassium phosphate buffer and inoculated immediately with zoospores. Four days after inoculation, the stem of each seedling was plated in 0.5-cm segments on PARP medium to determine percent infection. Values with the same letter are not significantly different according to Duncan's multiple range test ($P = 0.05$).

[z] Values for PO_3 meq/L were determined by dividing micrograms per milliliter by the conversion factors: 82 (H_3PO_3) or 132 (fosetyl-Na).

These results appear to controvert Fenn's Table 4, specifically, by showing that the addition of phosphate improves inhibition against *P. palmivora*. Dolan noted this discrepancy with the results obtained from the similar study by Fenn, concluding on page 977 only that more research is warranted:

> The enhanced level of control of *P. palmivora* in vivo in the presence of increasing levels of phosphate was unexpected. It contradicted findings obtained with the interaction between *P. cinnamomi* and *Persea indicia*, where phosphate was shown to reduce the efficacy of both compounds [here citing the work by Fenn and Coffey]. This indicates that phosphate influence on host and fungal metabolism may be an important factor affecting the efficacy of phosphonate fungicides. The relationship between phosphate concentration in tissues host parasite metabolism, and the mode of action of phosphonate fungicides could be complex. *There is need for additional research in this area to clarify the role of the host in these interactions* [emphasis added].

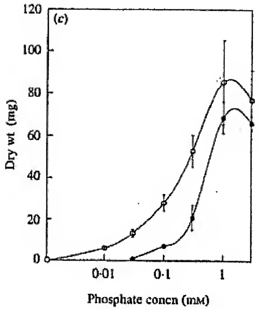
Page 977, Column 2, lines 1-10 of Dolan.

Thus, the Examiner's own references admit that they did not understand the phenomenon and could not produce consistent results, and that more research was warranted. At most, Dolan and Fenn disclosed that the relationship between

phosphate and phosphite concentrations and their effects on infection inhibition may be very complex. Therefore, there is no clear teaching in either Dolan, Fenn, or both that would motivate one of ordinary skills to modify the composition taught in these two references by increasing the concentration of both phosphate and phosphite in order to arrive at the composition presently claimed by Applicant.

Indeed, another reference of record, Griffith, which is not cited by the Examiner in the instant Office Action attempts to explain why Fenn and Dolan contradict one another. J. M. Griffith, M.D. Coffey, and B.R. Grant 1993, "Phosphonate inhibition as a function of phosphate concentration in isolates of *Phytophthora palmivora*," J. OF GENERAL MICROBIOL., 139: 2109-2116 (Griffith, Coffey &Grant). Griffith's results came from the same *P. palmivora* organism that was also the subject of the Dolan work.

In Griffith, *P. palmivora* was grown on medium that was enriched with phosphate at concentrations ranging up to a maximum of 1 mM. A "control" was performed for each phosphate concentration, and growth of these populations at each concentration were compared to growth on media that was also enriched with 1 mM phosphonate. These are extremely dilute concentrations of phosphate and phosphonate. Fig. 3 of Griffith shows that the relative inhibition effect which is caused by combining phosphonate with phosphate diminishes towards 1 mM. Griffith also discusses in Fig. 1(c) with regard to a mutant *P. palmivora* strain that is resistant to phosphonate. Fig. 1(c) is replicated below:



The Examiner can see from the above Fig. 1(c) that the observed inhibitory effect diminishes above 1 mM of phosphate concentration. Griffith also states in the discussion of Fig. 1(c) on page 2112 (discussing isolate P7228):

> However, at higher levels of phosphonate (0.3 mM and above) phosphonate was less inhibitory to growth, and resistance to the effects of this anion was clearly demonstrated.

The overall trend as to the diminishing inhibition effect with increasing phosphate content is true with respect to all isolates in the Griffin study, which states on page 2113 that the upper limits for the observed effect were in the range of from 1 mM to 3 mM:

> However, when Pi_e (phosphate content in the media) did not limit growth, at 1 mM and 3 mM, the P376 and P7228 strains accumulated more Pi (internal phosphate content in the cells) . . . than P113)

It will be appreciated that the P376 strain is one of the two mutant strains resistant to phosphonates that Dolan investigated, and that Griffith reports a much more thorough investigation. In Dolan, the levels of phosphate and phosphonate used were 10 mM and lower, which are also well below the concentrations that are now claimed.

Other work by Griffith shows that the metabolic interaction is more complex than one might otherwise imagine. The following Table is copied from J.M Griffith, R. H. Smillie, J.O. Niere and B. R. Grant, 1989 Effect of phosphate on the toxicity of phosphonate in *Phytophthora palmivora*, ARCH. MICROBIOL 152:425-429

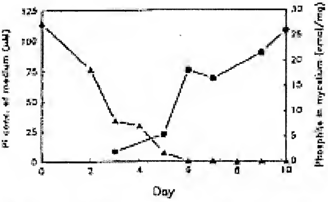


Fig. 1. The uptake of phosphite and the utilization of P_i by *Phytophthora palmivora* during growth in LPR medium containing 1 mM phosphite. P_i and phosphite concentrations were determined by ion chromatography as described in Methods. P_i in medium (▲——▲); phosphite in mycelium (●——●)

Griffith explains the significance of Fig. 1:

> Analysis of the phosphite [phosphonate] content of the mycellium grown in LPR medium in the presence of 1 mM phosphite (the concentration used by Fenn and Coffey in q1984) showed that there was an abrupt increase in the level of phosphite entering the mycellium after Pi [phosphate] had been depleted from the medium at day 6 (Fig. 1).

This is shown above in Fig. 1 where the curve on the left hand side represents diminishing phosphate content in the growth medium, and the curve on the right hand side represents phosphonate that has entered the fungal cells of *P. palmivora*. At these concentrations, the phosphonate does not start to work until the phosphate is depleted. This explains, for example, why "[p]hosphates have also been considered to be a competitive inhibitor for phosphonate assimilation, thus inhibiting the ability of

phosphonates to protect against fungus attack." U.S. 5,997,910, column 2, lines 57-60. But this is presented as a basis in support of patentability where the art shows generally that phosphates should <u>not</u> be mixed with phosphonates to achieve an antifungal effect.

Furthermore, Claim 2, as amended, recites a pH range of from 5 to 7, which is not taught or suggested by any of the cited references. Thus, Claim 2, for this reason alone, is not obvious over the cited art.

In summary, at the time of the present invention, the fungicidal or growth effects of relatively high concentrations of phosphate and phosphonate such as those claimed in the instant claims were not well understood. Indeed, Applicant has discovered that higher concentrations according to the claimed "effective amounts" produce an effect that differs in kind from what Fenn, Dolan and Griffith did. Thus, the claimed invention is not rendered obvious by Fenn and Dolan. Withdrawal of the 103 rejections is respectfully requested.

IV. Rejections of Claims 1, 2, 6 and 12 under 35 U.S.C. § 103(a)

Claims 1, 2, 6 and 12 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Barlet-5070083, Ducret et al. 4139616, Horriere et al. 5169646, Lovatt 5514200, Vetanovetz et al. 53905418 and Smilie et al. 1989. Applicant respectfully disagrees because substantial differences exist between the cited references and the instant invention and these differences are not obvious to one of ordinary skills in the art at the time of the present invention.

The Examiner reasons that the above cited references individually disclose the phosphonate or phosphate salts, and that Smilie teaches that the effectiveness of phosphite salts can be enhanced by phosphates. Applicant disagrees. As the discussion on page 924 of Smilie indicates, at the time of Applicant's invention, there had been contradictory results with respect to the effects of phosphate and phosphite in treating or preventing infection by difference species of fungi, or "different isolates of a given species." See page 924 of Smilie.

The Examiner appears to rely on the "obvious to try" rationale in rejecting the instant claims. However, as the Patent Office has made clear in the Examination

Guidelines, to reject a claim based on this rationale, Office personnel must first resolve the *Graham* factual inquiries, and then articulate the following:

(1) a finding that at the time of the invention, there had been a recognized problem or need in the art, which may include a design need or market pressure to solve a problem;

(2) a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem;

(3) a finding that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success; and

(4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in KSR International Co. v. Teleflex Inc., Federal Register, Vol. 72, No. 195, 57526-35, 57526 (October 10, 2007).

Note the requirement in item (2) above which requires a finite number of identified, predictable potential solutions to the recognized need or problem. Even if we assume that the combination of the cited references do teach the use of phosphite and phosphate in a fungicidal composition, none of the references, either alone or in combination, teaches or suggests the concentration range as now recited by Applicant's Claims. At the time of Applicant's invention, there existed almost infinite number of possible combination of phosphite and phosphate concentrations that could be tried before one of ordinary skill could arrive at Applicant's invention. Therefore, the 'obvious to try" rationale can not be properly applied in the instant case. Withdrawal of the rejections is respectfully requested.

V. Double Patenting Rejections

Claims 1-14 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent 6,509,041. Applicant disagrees with the Examiner that the instant claims are rendered obvious by claims 1-12 of U.S. Patent 6,509,041. However, Applicant recognizes that a timely

filed Terminal Disclaimer may overcome such a rejection, and will timely submit a Terminal Disclaimer if necessary.

VI. Supplemental Oath

Applicant will provide the supplemental Oath should this case be found allowable.

For the foregoing reasons, Applicant's attorney respectfully submits that the claims are worthy of allowance. Applicant believes no additional fees are due, however, if any additional fee is deemed necessary in connection with this Response, please charge Deposit Account No. 12–0600.

Respectfully submitted

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